APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: August 2003
Profile Status: Third Draft Pre-Public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 30
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] ppm

Reference: Adams EM, Spencer HC, Rowe VK, et al. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch Ind Hyg Occup Med 6:50-66.

Experimental design: Groups of Wistar rats (15–25 males, 15–23 females) were exposed to vapors of carbon tetrachloride (5, 10, 25, 50, 100, 200, and 400 ppm) for 173–205 days (5 days/week, 7 hours/day). Following exposure, clinical signs (no details provided), hematological (prothrombin time), and biochemical indices (blood urea nitrogen, phospholipid, esterified cholesterol) were monitored. Gross necropsy was performed and organ weights were determined. Histopathological examination was also performed.

Effects noted in study and corresponding doses: Fatty degeneration of the liver and increased liver weight were evident at concentrations of ≥10 ppm and hepatic cirrhosis and pathology of the renal tubular epithelium occurred at ≥50 ppm. No effects were observed in the 5 ppm exposure group for any of the parameters measured.

Dose and end point used for MRL derivation: A concentration of 5 ppm was used to derive the MRL, based on the absence of liver effects. This concentration was converted to a duration-adjusted NOAEL of 1 ppm by adjusting for intermittent exposure (i.e., by multiplying by a factor of 0.21 for exposure 7/24 hours/day, 5/7 days/week).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Used EPA inhalation RfD guidance (equation 4-10). Value of lambda(A)/lambda(H) assumed to be 1.0.

Other additional studies or pertinent information which lend support to this MRL: Prendergast et al. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloromethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol Appl Pharmacol 10:270–289.

Groups of rats (15/dose, sex not specified) were continuously exposed to vapors of carbon tetrachloride (1 or 10 ppm) for 90 days. Following exposure, clinical signs, body weight, biochemical indices, (succinic dehydrogenase [SDH], lactic dehydrogenase [LDH], beta-hydroxybutyric dehydrogenase [beta-OHBD], glucose-6-phosphate dehydrogenase [G6PD]), and blood chemistry (total and differential leucocyte counts, hemoglobin, hematocrit) parameters were measured. Histological examinations of the heart, lung, liver, spleen, and kidneys were performed. Fatty degeneration of the liver was observed at concentrations of 10 ppm, but no effects were seen at 1 ppm. No treatment-related effects were seen in the other parameters measured. A NOAEL of 1 ppm is identified for this study.

An uncertainty factor of 3 for extrapolation from animals to humans was selected because rats are more sensitive to carbon tetrachloride toxicity than humans. Based on comparative PBPK modeling, Thrall et al. (2000) calculated that the metabolism of carbon tetrachloride—which is the basis for its toxicity—proceeds at a higher rate in rats compared to humans (see Section 3.4.3).

The intermediate-duration MRL of 0.03 ppm should also be protective for acute-duration inhalation exposures. In acute-duration studies in rats and guinea pigs, fatty degeneration of the liver was observed at 10 ppm, the lowest concentration tested (Adams et al. 1952).

Agency Contact (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: August 2003
Profile Status: Third Draft Pre-Public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 45
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] ppm

References: Japan Bioassay Research Center. 1998. Subchronic inhalation toxicity and carcinogenicity studies of carbon tetrachloride in F344 rats and BDF1 mice (Studies Nos. 0020, 0021, 0043, and 0044). Kanagawa, Japan Industrial Safety and Health Association, Japan Bioassay Research Center (Unpublished report to the Ministry of Labor). Hirasawa Hadano Kanagawa, 257 Japan. (In 2001, T. Matsushima provided additional data tables for these studies: organ weights, hematology, serum chemistry, urinalysis).

(Methods published in: Nagano K, Nishizawa T, Yamamoto S et al. 1998. Inhalation carcinogenesis studies of six halogenated hydrocarbons in rats and mice. In: Advances in the prevention of occupational respiratory diseases. Chiyotani K, Hosoda Y, Aizawa Y, eds. Elsevier Science B.V., 741-746.)

Experimental design: Groups of 50 male and 50 female F344/DuCrj rats were exposed (whole-body) to vapors of carbon tetrachloride (>99% pure) 6 hours/day, 5 days/week for 104 weeks. Rats were observed daily for clinical signs, behavioral changes, and mortality. Body weights were measured weekly for the first 13 weeks and every 4 weeks thereafter. Urinalysis was performed at the end of the dosing period. Hematology and serum chemistry were measured in blood samples taken during final euthanization after overnight fasting. All organs and tissues were examined for gross lesions, weighed, and fixed for histopathological analysis.

Effects noted in study and corresponding concentrations: No significant hepatic effects were noted at 5 ppm. At ≥25 ppm, significant hepatic effects were observed: statistically significant elevations relative liver weights, serum parameters (total bilirubin, SGOT, SGPT), and increased incidences of liver histopathology (fatty change, granulation, foci in the liver, deposition of ceroid, and serious effects such as fibrosis and cirrhosis). At 125 ppm, spleen weights relative to body weight were increased in females. The highest level, 125 ppm, was a cancer effect level in both sexes: hepatocellular adenomas in 21/50 males and 40/50 females and hepatocellular carcinoma in 32/50 male and 15/50 females. Chronic nephropathy was observed in all groups, including controls, but at greater severity at 25 ppm and above; proteinuria was also observed in all groups, but at higher severity in males treated at 5 ppm and females at 25 ppm and above. At 25 ppm, females had significant hematological changes (decreased hemoglobin, hematocrit, and lymphocyte counts and increased leukocyte and segmented neutrophil counts). Hemosiderin deposition was increased in the spleens of male rats at 5 ppm, although the incidence and severity of the splenic effect did not increase at higher concentrations.

Dose and end point used for MRL derivation: A NOAEL concentration of 5 ppm was used to derive the MRL, based upon the lack of hepatic effects (increased liver weight, serum enzymes, and liver histopathology) observed at the LOAEL of 25 ppm and above. The NOAEL of 5 ppm was adjusted for intermittent exposure by multiplying by a factor of 0.18 (6/24 hours/day x 5/7days/week), resulting in a duration-adjusted LOAEL of 0.9 ppm.

[X] NOAEL [] LOAEL

Uncertainty Factors used in MRL derivation:

[] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Used EPA inhalation RfD guidance (equation 4-10). Value of lambda(A)/lambda(H) assumed to be 1.0.

Other additional studies or pertinent information which lend support to this MRL: A study in BDF1 mice was conducted concurrently with the rat study under the same experimental conditions. In mice, there is some uncertainty as to the apparent NOAEL of 5 ppm because the control values for serum chemistry parameters in males were unusually high compared to the companion subchronic study (no historical control values were available). The target organs identified at 25 ppm in mice were similar to those identified in rats. Protein casts were observed in males and urinalysis values were altered in both sexes (decreased pH and ketone bodies in both sexes and increased urobilinogen and occult blood in females). The incidence of extramedullary hematopoiesis in the spleen was increased in both sexes. Severe nonneoplastic hepatic effects included increased liver weights, degeneration, cyst, deposition of ceroid, increased serum enzymes, cholesterol, bilirubin in both sexes, and thrombus and necrosis in females. At 25 ppm, the following cancer effects were noted: hepatocellular adenoma in 27/50 males and 7/50 females, hepatocellular carcinoma in 42/50 males and 33/50 females, and adrenal pheochromocytoma in 16/50 males. The adrenal tumor was found in 22/49 females treated at 125 ppm.

The companion 13-week inhalation bioassays in rats and mice did not report a no-effect level. In rats, the lowest exposure level, 10 ppm, was a LOAEL for statistically-significant hepatic effects: increased granulation in both sexes, increased absolute liver weight in females, and increased relative liver weight in males. The LOAEL in the mouse assay was also 10 ppm for undefined cytological alterations in the livers of males.

The intermediate-duration study of Adams et al. (1952), which was used as the basis for the intermediate inhalation MRL, reported a NOAEL of 5 ppm and a LOAEL of 10 ppm for fatty degeneration of the liver in Wistar rats. .

An uncertainty factor of 3 for extrapolation from animals to humans was selected because rats are more sensitive to carbon tetrachloride toxicity than humans. Based on comparative PBPK modeling, Thrall et al. (2000) calculated that the metabolism of carbon tetrachloride—which is the basis for its toxicity—proceeds at a higher rate in rats compared to humans (see Section 3.4.3).

Agency Contact (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: August 2003
Profile Status: Third Draft Pre-Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: Smialowicz RJ, Simmons JE, Luebke RW, et al. 1991. Immunotoxicologic assessment of subacute exposure of rats to carbon tetrachloride with comparison to hepatotoxicity and nephrotoxicity. Fundam Appl Toxicol 17:186-196.

Experimental design: Groups of 5–6 male Fischer 344 rats were dosed by gavage for 10 consecutive days with 0, 5, 10, 20, or 40 mg/kg/day of carbon tetrachloride in corn oil. Serum chemistry profiles, hepatic cytochrome P-450 content and activity, and kidney and liver organ weight and histopathology were assessed. Various immune function parameters were also examined in these animals, and in another set exposed to 40, 80, or 160 mg/kg/day.

Effects noted in study and corresponding doses: No significant renotoxic or immunotoxic effects were observed at any dose. In the centrilobular region of the liver, minimal vacuolar degeneration was detectable at 5 mg/kg/day and minimal hepatocellular necrosis was noted in some rats at 10 mg/kg/day, with both effects demonstrating a clear dose response in terms of severity. Serum alanine and aspartate aminotransferase levels were significantly ($p<0.01$–0.05) elevated to levels 146–543% those of controls as doses of 20 and 40 mg/kg/day, and relative liver weights was increased by 17.7 ($p<0.01$) at 40 mg/kg/day.

Dose and end point used for MRL derivation: 5 mg/kg/day; minimal vacuolar degeneration of centrilobular hepatocytes.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: One or more of these hepatic effects have also been reported to occur at doses as low as 10–20 mg/kg/day in several other rat studies (Bruckner et al. 1986; Kim et al. 1990b; Korsrud et al. 1972). These were the lowest doses examined in those studies, thus supporting the present study where the effects were just detectable at the 5–10 mg/kg/day dose level.

An uncertainty factor of 3 for extrapolation from animals to humans was selected because rats are more sensitive to carbon tetrachloride toxicity than humans. Based on comparative PBPK modeling, Thrall et al. (2000) calculated that the metabolism of carbon tetrachloride—which is the basis for its hepatotoxicity—proceeds at a higher rate in rats compared to humans (see Section 3.4.3).

Agency Contact (Chemical Manager): Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Carbon Tetrachloride
CAS Number: 56-23-5
Date: August 2003
Profile Status: Third Draft Pre-Public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 42
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Bruckner JV, MacKenzi WF, Muralidhara S. et al. 1986. Oral toxicity of carbon tetrachloride: acute, subacute and subchronic studies in rats. Fundam Appl Toxicol 6:16–34.

Experimental design: Male Sprague-Dawley rats (15–16/dose) were administered carbon tetrachloride (0, 1, 10, or 33 mg/kg) in corn oil by gavage for 12 weeks (5 days/week). Following treatment, body weight was monitored. Sorbitol dehydrogenase (SDH), ornithine carbamyl transferase (OCT), and alanine aminotransferase (ALT) activities in serum were measured. Blood urea nitrogen (BUN) levels in serum were also measured. Histopathological examination of the liver and kidneys was performed.

Effects noted in study and corresponding doses: Mild centrilobular vacuolization was observed and there were statistically significant increases in serum SDH activity at dose levels of 10 mg/kg/day. Cirrhosis and increased serum enzyme (OCT, SDH, ALT) activities were also reported at the highest dose tested (33 mg/kg/day).

Dose and end point used for MRL derivation: A dose of 1 mg/kg/day was used to derive the MRL, based on the absence of liver effects. This dose was converted to 0.71 mg/kg/day, incorporating adjustments for intermittent exposure (5 days/week).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: Condie et al. 1986. Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD–1 mice: Corn oil vs Tween 60 aqueous emulsion. Fundam Appl Toxicol 7:199-206.

Groups of CD–1 mice (9–12/sex) were administered carbon tetrachlordide (0, 1.2, 12, or 120 mg/kg/day) in corn oil by gavage once per day, 5 days/week for 90 days. Body weights were monitored during the exposure period. Biochemical (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH]) activities increased at dose levels of 12 mg/kg/day or greater. Histopathological changes were also observed in the liver.

Hepatocellular cytomegaly, fat, and necrosis were seen at dose level 12 mg/kg/day and necrosis also occurred in the 120 mg/kg/day dose group. A NOAEL of 1.2 mg/kg/day is identified for this study.

Hayes et al. 1986. Acute, 14-day repeated dosing and 9-day subchronic toxicity studies of carbon tetrachloride in CD-1 mice. Fundam Appl Toxicol 7:454-463.

Twenty CD-1 mice both sexes received carbon tetrachloride (0, 12, 120, 540, and 1,200 mg/kg/day) in corn oil by gavage for 90 days. After treatment, clinical signs and body weight were monitored. Gross necropsy was performed and organ weights were determined. Hematological, biochemical, and histopathological examinations as well as urinalysis were done. The authors reported there were no consistent effects on hemoglobin, hematocrit, leucocyte, erythrocyte, and platelet counts as well as prothrombin times and plasma fibrinogen levels. It should be noted that the study did not provide data for evaluation. Serum hepatic enzyme activity (lactate dehydrogenase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase) increase at dose levels of 12 mg/kg/day or greater. Blood glucose levels decreased at comparable dose levels. Liver weights increased and central necrosis was evident in all dose groups. No treatment-related histological lesions of the kidneys were observed. A LOAEL of 12 mg/kg/day was identified for this study.

An uncertainty factor of 3 for extrapolation from animals to humans was selected because rats are more sensitive to carbon tetrachloride toxicity than humans. Based on comparative PBPK modeling, Thrall et al. (2000) calculated that the metabolism of carbon tetrachloride—which is the basis for its hepatotoxicity—proceeds at a higher rate in rats compared to humans (see Section 3.4.3).

Agency Contact (Chemical Manager): Obaid Faroon

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

TABLE 3-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

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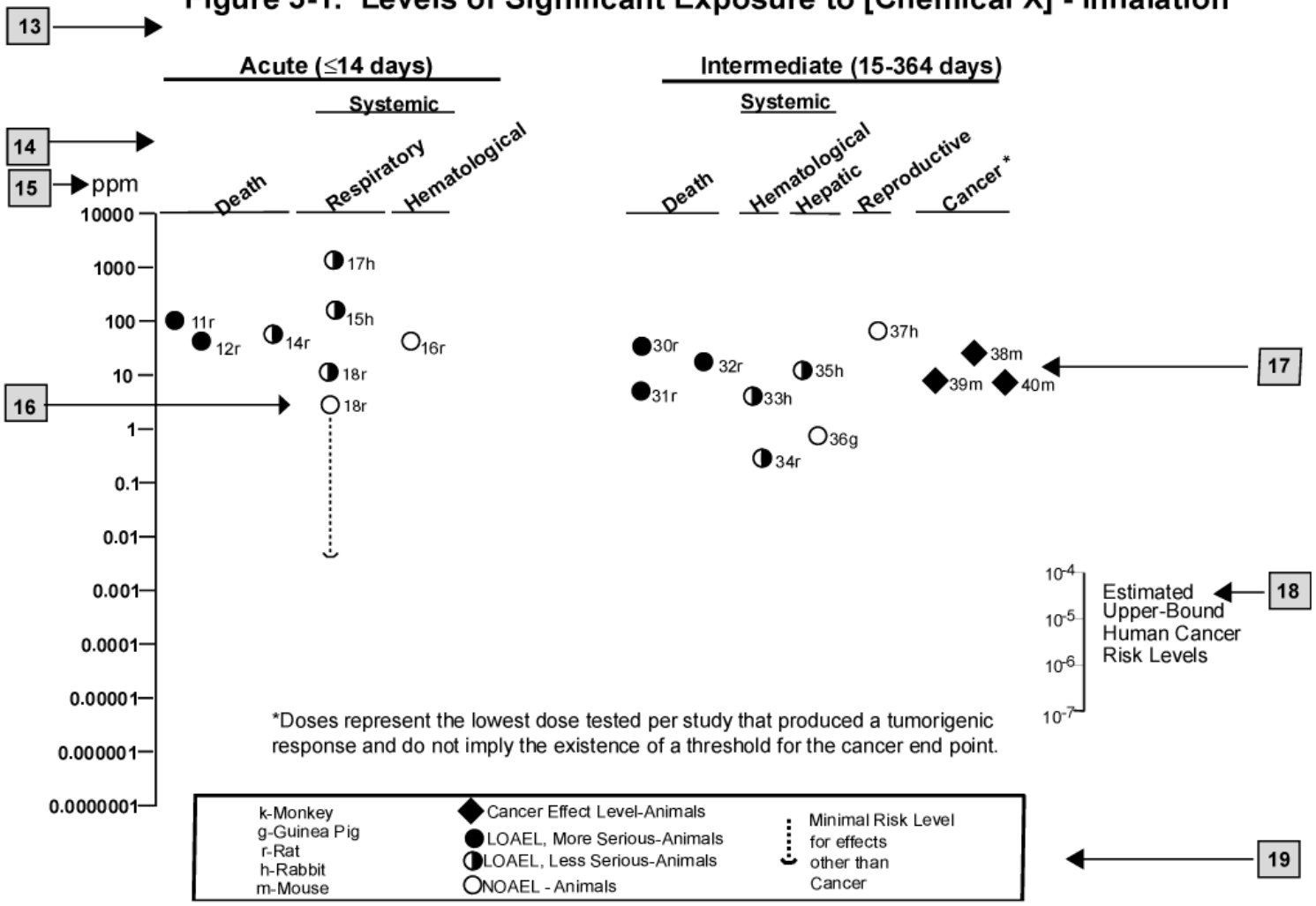
[a]The number corresponds to entries in Figure 3-1.

[b]Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram

mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes

PEL	permissible exposure limit
pg	pictogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result